TITLE: A Randomized Multicenter Phase II Study Using 2-1[Hexyloxyethyl]-2-Devinylpyropheophorbide-A (HPPH) with PDT versus Standard of Care Surgery for Patients with T1/T2 N0 Squamous Cell Carcinoma of the Oral Cavity

Roswell Park Cancer Institute

Study Number: **I 33616** **NCT03090412**

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IND Holder: **Roswell Park Cancer Institute**

Principal Investigator:

Jon Chan MD
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, New York 14263
716-845-3158
Jon.Chan@RoswellPark.org

Sponsor: **Roswell Park Cancer Institute**

Industry Supporter: **Photolitec LLC**

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RPCI Study Contacts

FOR NETWORK SITES: Please contact the RPCI Network Monitor for any study-related questions regarding sample handling, processing or shipping.

Study Personnel outside of RPCI-CRS who will be housing essential documents or receiving, analyzing or storing biological samples.

Name	Institution	Email	Role
Gal Shafirstein, DSc	Roswell Park Cancer Institute, Buffalo, NY	Gal.Shafirstein@RoswellPark.org	Treatment Planning
Sandra Gollnick, PhD	Roswell Park Cancer Institute, Buffalo, NY	Sandra.Gollnick@RoswellPark.org	
David Bellnier, PhD	Roswell Park Cancer Institute, Buffalo, NY	David.Bellnier@RoswellPark.org	Drug uptake
Alan Hutson, PhD	Roswell Park Cancer Institute, Buffalo, NY	Alan.Hutson@RoswellPark.org	Statistical Analysis
Joseph D. Tario,Jr.PhD	Roswell Park Cancer Institute, Buffalo, NY	joseph.tario@RoswellPark.org	Flow Cytometry

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SYNOPSIS

Title / Phase	A Randomized Multicenter Phase II Study Using 2-1[Hexyloxyethyl]-2-Devinylpyropheophorbide-A (HPPH) with PDT versus Standard of Care Surgery for Patients with T1/T2 N0 Squamous Cell Carcinoma of the Oral Cavity
Roswell Park Cancer Institute Study Number	I 33616
Roswell Park Cancer Institute Investigator	Jon Chan, MD
Sponsor	Roswell Park Cancer Institute
Industry Supporter	Photolitec LLC
Study Drug	HPPH (2-1[hexyloxyethyl]-2-devinylpyropheophorbide-a)
Objectives	**Primary:** • To test the non-inferiority of PDT to standard of care surgery by comparing the rate of tumor response after PDT to those observed after surgery, at 24 months post treatment. **Secondary:** • To determine quality of life (QoL) at 6, 12, 18, and 24 months post PDT or surgery. • To assess the toxicity using the CTEP NCI Common Terminology Criteria for Adverse Events (CTCAE Version 4.0). **Tertiary:** • Immune markers (T cells). • To investigate the correlation of diffuse reflectance optical spectroscopy with tumor response to PDT (**Appendix B**).
Study Design	• This is an open-label, randomized, multicenter Phase II study of HPPH-mediated PDT in patients with lesions that are diagnosed as previously untreated T1 N0 or T2 N0 SCC of the oral cavity. 114 participants will be randomized (1:1) to surgery (57) or PDT with HPPH (57). The randomization will be done at RPCI by the biostatistician. • Participants will be treated on an outpatient basis. Rarely, participants may require hospitalization, but this will be decided on a case by case basis. All participants will meet the inclusion and exclusion criteria. • Participants randomized to PDT with HPPH will be administered a single dose of HPPH at 4 mg/m^2 via slow intravenous (IV) infusion over 1 hour. Approximately 1 day later, the target tumor will be illuminated with a 665-nm laser light at dose of 140 Joules/cm^2 delivered at a fluence rate of 150 mW/cm^2. The participants will be scheduled to have clinical examination at 1 week, 4 - 6 weeks, 12-16 weeks, and at 24 months post therapy. Pathological evaluation will be conducted by taking a 3-mm punch biopsy from the treated region during the 12-16 weeks clinical visit. In the event that a suspicious lesion is observed, the participants will be scheduled for a biopsy at the discretion of the treating physician. Participants will receive standard curative therapy 6 weeks after failing to respond to PDT with HPPH. Tumor response will be determined according to the revised response evaluation criteria in solid tumors (RECIST v1.1).

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Target Accrual and Study Duration	A maximum of 114 participants at 3 sites, including RPCI, will be enrolled. Accrual is expected to take up to 4 years. Each participant is expected to be on the study for two years and will be followed according to NCCN guidelines.
Study Procedures	**Disease Evaluation:** Baseline and as per the NCCN guidelines for T1/T2 SCC of the head and neck. **Quality of Life Questionnaire:** Baseline, post treatment at 12 - 16 weeks and 6, 12, 18, and 24 months. **Hematology:** Baseline. **Chemistry:** Baseline. **Performance Status:** Baseline, post treatment at 12 - 16 weeks, and at follow-up visits. **Clinical Examination:** Baseline and post treatment at 1 week, 4 - 6 weeks, 12 - 16 weeks. We will follow the subjects according to the NCCN guidelines for patients with T1/T2 SCC, i.e. every 3 – 4 months (year 1), 3 – 6 months (year 2). **Vital Signs:** Baseline, Day 0, post treatment at 1 week, 4 - 6 weeks, 12 - 16 weeks, and at follow-up visits. **HPPH Infusion:** Day 0 **Blood Samples:** Day 0, 7, and 4-6 weeks **Optical Spectroscopy:** Day 1 **Laser:** Day 1 **Adverse Events:** From administration of study drug or surgery until 30 days after receiving study drug or surgery.
Statistical Analysis	The primary objective of this study is to test the non-inferiority of PDT to standard of care by comparing the rate of tumor response after PDT to those obtained after surgery. This is a randomized multicenter Phase II trial with PDT with HPPH for the treatment of T1/T2 N0 primary tumors of the oral cavity. The design is based on a test for non-inferiority of PDT compared to standard of care with regards to tumor response. Justification for use of a non-inferiority trial is that PDT may be viewed as a potential replacement for standard of care if it is established as less toxic than the standard of care yet still providing acceptable efficacy. **Sample Size Determination:** The samples sizes of the trial are set at 57 in each of the standard of care and PDT groups. With the proposed sample sizes, there is approximately 80% power associated with the non-inferiority test when the true tumor response probabilities are equal to 85% in both groups. **Randomization:** The randomization scheme will be generated at RPCI by the biostatistician. 114 participants will be randomized at a ratio of 1:1 to be treated with either standard of care surgery (57) or PDT with HPPH (57). **Efficacy Analysis:** Objective tumor response will be tabulated overall. All participants who randomized to PDT treatment or surgery will be evaluable for response. Tumor response will be determined by comparing the photographs of the treated site (with reference ruler) before and after PDT or surgery. **Safety Analysis:** The frequency of toxicities will be tabulated by grade across all cycles. All participants who randomized to HPPH PDT will be considered evaluable for toxicity.

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Participant Name (Network sites use participant initials)**:**_____

Medical Record No. (Network sites use participant ID)**:**_____

Title: A Randomized Multicenter Phase II Study Using 2-1[Hexyloxyethyl]-2-Devinylpyropheophorbide-A (HPPH) with PDT versus Standard of Care Surgery for Patients with T1/T2 N0 Squamous Cell Carcinoma of the Oral Cavity

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "YES or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Age ≥ 18 years of age.	
☐	☐	☐	2. Have an ECOG Performance Status of ≤ 2. Refer to **Appendix D**.	
☐	☐	☐	3. Participants with previously untreated T1/T2 N0 squamous cell carcinoma of the oral cavity with or without extension to the oropharynx.	
☐	☐	☐	4. Histologically confirmed squamous cell carcinoma of the target tumor(s).	
☐	☐	☐	5. Tumor thickness is 4 mm or less (measured clinically and/or by CT or MRI scan).	
☐	☐	☐	6. CT or MRI of the neck to confirm staging.	
☐	☐	☐	7. Tumor accessible for unrestricted illumination for photodynamic therapy (PDT) (accessibility as determined by the physician).	
☐	☐	☐	8. Life expectancy of at least 12 months in the judgment of the physician.	
☐	☐	☐	9. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.	
☐	☐	☐	10. Participant or legal representative must understand the investigational nature of this study and sign an Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Study participant meets all entry criteria: ☐ **Yes** ☐ **No**

Investigator Signature: _____ **Date:** _____

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Participant Name (Network sites use participant initials)**:**_____

Medical Record No.: (Network sites use participant ID)**:**_____

Title: A Randomized Multicenter Phase II Study Using 2-1[Hexyloxyethyl]-2-Devinylpyropheophorbide-A (HPPH) with PDT versus Standard of Care Surgery for Patients with T1/T2 N0 Squamous Cell Carcinoma of the Oral Cavity

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "NO" or "N/A" for participant enrollment**	**Date**
☐	☐	☐	1. Those who have had chemotherapy or radiotherapy or targeted agents within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.	
☐	☐	☐	2. Those with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.	
☐	☐	☐	3. Those with porphyria or with known hypersensitivity to porphyrins or porphyrin-like compounds.	
☐	☐	☐	4. WBC < 4,000.	
☐	☐	☐	5. Those with impaired renal and/or hepatic function, total serum bilirubin > 2 mg/dL, serum creatinine > 2 mg/dL, alkaline phosphatase (hepatic) or SGOT > 3 times the upper normal limit.	
☐	☐	☐	6. Diagnostic biopsy reveals perineural invasion (PNI) and/or lymphovascular invasion (LVI).	
☐	☐	☐	7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	
☐	☐	☐	8. Nodal disease as detected by clinical exam or CT.	
☐	☐	☐	9. Pregnant or nursing females.	
☐	☐	☐	10. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	11. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.	
☐	☐	☐	12. Received an investigational agent within 30 days prior to enrollment.	
☐	☐	☐	13. Trismus or compromised airway.	
☐	☐	☐	14. Previous therapy to the target tumor site.	

Study participant meets all entry criteria: ☐ **Yes** ☐ **No**

Investigator Signature: _____ **Date:** _____

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1 BACKGROUND

1.1 CANCER OF THE ORAL CAVITY

Cancer of the head and neck is the sixth most prevalent cancer worldwide, with an incidence exceeding half a million cases annually.[1] The most recent data from the NCI Surveillance, Epidemiology, and End Results (SEER) Program predicted that 48,330 men and women (34,780 men and 13,550 women) would be diagnosed with and 9,750 men and women would die of cancer of the oral cavity and pharynx in 2016.[2] These numbers represent an estimated 16.8% increase in the incident and 23.57% in death rate when compared to the published statistics in 2013 (41,380 were diagnosed and 7,890 were expected to die from head and neck cancer).[3] The steady increase in incidents and death rate suggest that there is an urgent need to improve the treatment for this specific cancer.

1.2 STANDARD TREATMENT FOR EARLY STAGE CANCER OF THE ORAL CAVITY

Surgery and radiotherapy are standard treatment modalities for T1/T2 oral cavity cancer (OCC).[4] Several studies demonstrated that surgery is the preferred treatment for oral squamous cell carcinoma (SCC), yielding superior 5-year survival rates when compared to radiation therapy.[4,5] Furthermore, the sequelae of radiation therapy such as xerostomia, chronic dental decay and risk of mandibular osteonecrosis remain long after the patient is "cured," reducing the patients' quality of life (QoL).[6]

Effective surgical treatment of OCC requires wide local resection of the primary tumor with clear surgical margins. In order to secure tumor free margins the surgical procedures remove additional functional tissue often affecting speech and swallowing. **Following the initial surgery, the risk of local recurrences is as high as 20%.**[7-9] Local recurrences are usually treated with further surgery, requiring more mucosal resection. Patients that have been cured with standard therapy also have a significant risk of developing second primary tumors, which has been associated with poor prognosis.[10-12] Treatment of second primaries will increase patient morbidity. Currently, younger patients are being diagnosed with oral cancer, and their QoL is severely affected by standard of care therapies.[6,13] It is important to provide this patient population with a first line therapy that will not cause irreversible long-term toxicities, and if failed, can be followed with standard surgery to improve the chance of cure.

Photodynamic therapy (PDT) can result in good local control of early stage OCC with minimal loss of tissue volume and excellent long-term healing that is expected to improve QoL.[14-16] Our experience (including our collaborator, Dr. Biel) suggest that patients who failed to respond to PDT can be safely salvaged with standard surgery.[17,18]

1.3 PHOTODYNAMIC THERAPY FOR EARLY STAGE HEAD AND NECK CANCER

Numerous studies over the past 25 years have used photodynamic therapy (PDT) to treat early stage oral and oropharyngeal carcinomas. While many of the early studies were single site with small numbers of patients, in 2004 a major prospective multi-center trial was conducted using mTHPC-PDT to treat early (carcinoma in situ, Cis -T2) disease.[19] A total of 114 patients were

treated with an overall complete tumor response (CR) of 85% which was maintained in 85% of the patients for 1 year. In 2010 Biel reported the cumulative results of treatment of Cis-T1 carcinomas with Photofrin-PDT to be a CR of 94% with a 5 year response of 90%.[20] A review of the literature showed that, between 1990 and 2013, 729 patients were treated with PDT with a cumulative overall tumor response rate of 0.85 (Table 1). Importantly, healing was reported to be excellent and salvage treatment carried out by either surgery or repeated PDT resulted in 100% CR.[20] Side effects were largely limited to photosensitivity and pain at the treatment site, which was easily managed by analgesics. Photosensitivity was more pronounced and last longer when Photofrin was used; [20] however second generation photosensitizers, mTHPC and HPPH, resulted in only mild-moderate photosensitivity.[21] Importantly, several studies have shown that PDT results in fewer treatment-associated morbidities that conventional therapies, including little to no nerve damage, minimal scarring and retention of organ function.[18-22] The organ sparing nature of PDT has the potential to result in fewer complex reconstructive surgical interventions.

Although no direct comparison studies showing superiority or at least non-inferiority to the standard of care (SoC) modalities of surgery or radiotherapy have been conducted, single site and retrospective studies have compared responses after PDT vs. surgery in early stage oral cancer. Karakullukcu et al. [23] found no significant difference in treatment outcome between PDT (n=55) and surgical removal (n=43) of T1s-T2 oral cancer. A multicenter retrospective meta-analysis of 126 PDT and 56 surgical T1 cases demonstrated a comparable CR and no significant differences in overall survival were observed between the two modalities.[24]
Thus, the breadth of experience in treatment of early stage oral cancer with PDT suggests that early oral malignancies are amenable to this non-invasive therapy and that the therapy can result in comparable outcomes to the SoC. However, these findings need to be confirmed in a multicenter, randomized clinical trial.

Table 1. Clinical studies of PDT of early oral and oropharyngeal carcinomas.

Study	Year	*n**	*T*	PS	CR	PR	NR	Ratio CR
Feyh et al. [25,26]	1990, 1993	15	T1-T2	Photofrin	13	2		1.00
Grant et al. [27]	1993	11	T1	Photofrin	10	1		0.91
Grant et al. [28]	1993	4	T1	ALA	3	1		0.75
Fan et al. [29]	1996	18	Cis-T1	ALA	14	3	1	0.78
Savary et al. [30]	1997	4	Cis-T1	mTHPC	4			1.00
Fan et al. [31]	1997	20	Cis-T4	mTHPC	14		6	0.7
Schweitzer [32]	2001	10	Cis-T2	Photofrin	8	2		0.8
Kübler et al. [33]	2001	25	T1-T2	mTHPC	22	3		0.88
Dilkes et al. [34]	2003	17	T1-T3	mTHPC	15	2		0.53
Copper et al. [22]	2003	29	T1-T2	mTHPC	25	4		0.83
Hopper et al. [19]	2004	114	Cis-T2	mTHPC	97	17		0.85
Biel [20]	2010	138	Cis-T1	Photofrin	131	9		0.94
Rigual et al. [35]	2009	20	Cis-T1	Photofrin	19	1		0.95

Study	Year	*n**	*T*	PS	CR	PR	NR	Ratio CR
Schweitzer and Somers[36]	2010	30	Cis-T2	mTHPC	24	6		0.8
Jerjes et al. [37]	2011	38	T1-T2	mTHPC	22	10	6	0.58
de Visscher et al. [24]	2013	156	T1-T2	mTHPC	127	29		0.81
Karakullukcu et al. [23]	2013	55	T1-T2	mTHPC	49	6		0.89
Ikeda et al. [38]	2013	25	Cis-T2	Photofrin	24	1		0.96
Rigual et al. [18]	2013	17	T1-T2	HPPH	14	3		0.82
SUM		**729**			**619**	**97**	**13**	**0.85**

*n=number of patients; T=tumor size; PS=photosensitizer; CR=complete response; PR=partial response; NR=no response; mTHPC=m-tetrahydroxyphenylchlorin (Foscan®); HPPH-3-(1'-hexyloxyethyl) pyropheophorbide a.

While PDT with the FDA-approved drug porfimer sodium is a highly effective treatment modality, the persistence of porfimer sodium in skin and associated photosensitization necessitates complete protection from sunlight and other sources of bright light for periods up to 90 days. Further, porfimer sodium is activated by light at 630 nm, which is suboptimal for tissue penetration. These drawbacks have led to a search for other photosensitizers without these limitations.[39]

RPCI's PDT center evaluated over 400 new photosensitizers as possible successors to Photofrin®. HPPH was identified in a preclinical quantitative structure-activity relationship study to be the most effective photosensitizer among a series of homologues with different numbers of methylene groups on the ether function.[40]

1.4 PRECLINICAL STUDIES WITH HPPH

A detailed discussion of the preclinical pharmacology, pharmacokinetics, and toxicology of HPPH can be found in the Investigator's Brochure.

1.5 CLINICAL STUDIES: HPPH

1.5.1 PHARMACOKINETICS (PK)

A detailed description of the PK studies, results and analysis, can be found in section 5.2 of the Investigator Brochure.

One study in 25 cancer patients revealed estimated mean population α and β half-lives (95% confidence intervals) of 7.77 hours (3.46 - 17.6 hours) and 596 hours (120 - 2951 hours), respectively.[41] No metabolites were detected in serum. A more extensive study of skin photosensitivity in 48 patients receiving HPPH doses of 2.5 - 6 mg/m^2 and solar simulator light doses from 44.4 - 133.2 J/cm^2 demonstrated that one day after drug administration the highest drug and light doses elicited a response of only erythema without edema. With over 70 patients treated to date we have found that (a) HPPH at doses of 2.5 - 6 mg/m^2 has no systemic toxicity; (b) HPPH at doses of 3 mg/m^2 and higher (to 6 mg/m^2) approaches the effectiveness of Photofrin® (no head to head comparisons have yet been carried out), and (c) HPPH does not induce long-term cutaneous photosensitivity, based on in-house solar simulator testing and patient input.

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1.5.2 THE HPPH DOSE

In this protocol the participants will be treated with HPPH at fixed dose of 4 mg/m^2. This dose is based on 5 studies, balancing safety and efficacy considerations, where HPPH-PDT was employed in the treatment of esophageal cancer - 2 studies in obstructing disease and 3 studies in high grade dysplasia, CIS and early adenocarcinoma. The number of patients enrolled per HPPH dose was as follows: 11 at 6 mg/m^2, 3 at 5 mg/m^2, 36 at 4 mg/m^2 and 32 at 3 mg/m^2. All were treated with 150 Joules/cm^2. The percentages of SAEs possibly, probably and definitely related to PDT were in order 46%, 33%, 28% and 28%, respectively. Additionally, in the studies of high-grade dysplasia, CIS and early adenocarcinoma, 72% of complete responses were observed at 1 year at 3 and 4 mg/m^2 combined, while no complete responses were observed at 5 or 6 mg/m^2. There was no statistical difference in outcomes between 3 and 4 mg/m^2 (Nava et al., Lasers in Surg. Med. 43, 705-12, 2011).[42] The latter is likely due to photochemical oxygen depletion in tissue with high photosensitizer levels, which limits photodynamic action.

1.5.3 THE LIGHT FLUENCE RATE AND DOSE FOR EARLY STAGE HEAD AND NECK CANCER

Recently, RPCI has completed 3 Phase I studies of PDT with HPPH in the treatment of HNSCC. In the first study, (NCT00670397) PDT with HPPH was used intra-operatively in patients with resectable, primary or advanced recurrent SCC of the head and neck.[43] This was a dose escalation study, where the drug dose was 4 mg/m^2 and light dose was increased from 30 - 75 J/cm^2. In this study, no serious adverse event was reported. The treatment was found to be safe at the maximum light dose of 75 J/cm^2. Furthermore, major neurovascular structures and blood vessels were irradiated with the laser light during the PDT, but no carotid artery ruptures or cranial nerve injuries were observed, demonstrating that PDT with HPPH does not induce irreversible damage to healthy vital structures. This study also observed excellent healing of the overlaying skin in the 2 subjects that experienced skin burns as an adverse event. This healing was attributed to the fact that HPPH is not transported into fibroblasts.[44] Thus, the native tissue that replaces the cancer cells regains its normal functions, significantly limiting function loss and minimizing scar formation.

In other Phase I studies, PDT with HPPH was used for dysplasia and T1 squamous cell carcinoma (SCC) of the oral cavity and oropharynx. Both trials, carried out at RPCI from April 2008 to June 2012, used HPPH at a fixed, previously determined dose of 4 mg/m^2 administered systemically 20 – 28 hours before light delivery. In NCI-2010-02401 the light dose was escalated from 50 J/cm^2 to 75 J/cm^2, 100 J/cm^2 and 125 J/cm^2. In NCI-2010-01493 the light dose range was 100, 125 and 140 J/cm^2. Both trials had identical 3+3 designs, with an expanded cohort at 140 J/cm^2. Three courses of treatment were allowed for each oral lesion, with at least 6 weeks between treatments. Patients could have more than one lesion treated. The primary objectives were to establish the safety profile, to determine any dose-limiting toxicities (DLTs), and the maximum tolerated light dose (MTD). Secondary objectives were the determination of HPPH levels in blood and in the tumor tissue at the time of treatment, the extent of PDT-induced STAT3 crosslinking in the treated tissue, and the pathological treatment response as determined by biopsy at 3 months post treatment.

All patients who received PDT with HPPH reported the expected pain and edema at the treatment site, with pain lasting up to 4 weeks. Two patients in NCI-2010-02401 had Grade 3 edema at the application site at a light dose of 125 J/cm^2, and one experienced respiratory distress shortly after illumination. This patient had presented with severe trismus from prior therapy, which

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compromised precise light delivery and dosimetry to the lesion, which was located on the palate. The patient underwent a tracheostomy and recovered rapidly and completely without sequelae. This event, however, led to the closing of the protocol and addition of severe trismus as an exclusion criterion in NCI-2010-01493. Two patients in NCI-2010-01493 experienced Grade 3 edema at the application site at 140 J/cm^2, and one patient at that light dose experienced Grade 3 ulceration. These adverse effects were temporary and resolved completely. Most patients chose a liquid or pureed diet due to pain for several days after treatment, but no medical intervention to support alimentation was needed. Mild sunburn reactions due to non-compliance with sun-protection instructions were experienced in 1 patient in NCI-2010-02401 and 3 patients in NCI-2010-01493. An MTD was not reached at the highest planned dose level, but further escalation was forgone due to the danger of unacceptable swelling and ulceration.

The response to therapy for SCC is summarized in **Table 1** below.

Table 1. Response to Therapy for SCC

Light Dose, J/cm^2	No. of SCC Lesions (Responses)
50	1 (1 CR)
75	2 (1 CR, 1 SD)
100	2 (1 CR, 1 unevaluable)
125	1 (1 CR)
140	17(14 CR*, 1 PR, 2 SD)

*Two lesions had complete disappearance of carcinoma but had minor remaining focal dysplasia. CR=complete response, PR=Partial response, SD=stable disease, as defined in **Section 9.3** of this protocol.

The disease-free interval ranged from 5 to 40 months and follow-up is still ongoing. The CRs were also associated with increase in STAT3 crosslinking, which suggests that the responses were due to photodynamic reaction.[45-47]

The results of this study were recently published in Clinical Cancer Research (Rigual, Shafirstein et al. 2013).[18]

In this protocol the light fluence rate and dose will be fixed at 150 mW/cm^2 and 140 J/cm^2, respectively.

1.6 RISKS AND/OR BENEFITS

For participants that will have partial or complete response to PDT, the potential benefits include complete clinical regression of the tumor. Participants that do not respond to PDT may not benefit from this treatment. There is no guarantee of the outcome nor is it possible to predict whether or not the participant will respond to HPPH mediated PDT.

This is a Greater Than Minimal Risk study according to IRB criteria. The most likely potential risks associated with the PDT are short term edema and pain.

2 RATIONALE

Surgical resection and radiotherapy are front line therapies for T1 and T2 oral cavity cancer. However, these therapies are associated with multiple morbidities and impaired QoL issues such as alteration of speech, dysphagia and xerostomia. PDT, which involves the activation by light of

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a tumor-localized photosensitizer, has proven to be an effective local treatment for a range of solid tumors. It has the potential to become an effective first line treatment modality for this disease for the following reasons: it is minimally invasive, has low toxicity, is not associated with any long-term morbidity and is repeatable. Importantly, it allows the physician to reserve conventional, more toxic treatments such as radiotherapy and chemotherapy for later application, if needed.

The purpose of this multicenter study is to test the non-inferiority of PDT with HPPH to standard of care by comparing the rate of tumor response and QoL after PDT to those obtained after surgery in participants with previously untreated T1/T2 N0 SCC of the oral cavity.

Phase I studies have demonstrated that this treatment is safe. These studies also determined the safe drug and light dosages: 4 mg/m^2 and 100 - 140 J/cm^2, respectively. Data also suggest that early stage SCC may have excellent response to this therapy (see **Table 1**).

In our recent study with HPPH-PDT, all the patients with T1/T2 who failed to have CR to PDT were successfully salvaged with surgery.[18] Importantly, in patients with invasive disease who achieved only PR, the disease could be downgraded to dysplasia, thus minimizing salvage surgery. While all studies with HPPH-PDT to date have been Phase I studies, the response to PDT is swift and all patients, with few exceptions, have been assessed for response by pathological analysis.
We believe that PDT with HPPH is a viable option to treat patients with T1/T2, because:

- HPPH-PDT is expected to be an organ sparing treatment option, and failures can be salvaged with surgery.
- HPPH, at clinically effective antitumor doses, is associated with significantly reduced cutaneous photosensitivity that rapidly declines over several days.[41]
- The CR to HPPH-PDT is expected to be 85%, which would be comparable to cure rates after the initial surgery that is associated with 20% local recurrence. [7-9]
- Noninvasive optical spectroscopy has potential to serve as a surrogate reporter for tumor response to HPPH-PDT.[48]

Therefore, we hypothesize that patients may choose a treatment option, such as PDT with HPPH, if it provides non-inferior cure rate at the time of the initial treatment.

2.1 RATIONALE FOR ANCILLARY LABORATORY STUDIES

In the current study, immune cells will be collected from participants before and after PDT and tested for reactivity to the participant's tumor cells. These will only be collected from participants randomized to PDT with HPPH. Refer to **Appendix G.**

3 OBJECTIVES

3.1 PRIMARY OBJECTIVE

- To test the non-inferiority of PDT to standard of care surgery by comparing the rate of tumor response after PDT to those observed after surgery, at 24 months post treatment.

3.2 SECONDARY OBJECTIVES

- To determine quality of life (QoL) at 6, 12, 18, and 24 months post PDT or surgery.
- To assess the toxicity using the CTEP NCI Common Terminology Criteria for Adverse Events (CTCAE Version 4.0).

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3.3 TERTIARY OBJECTIVE

- Immune markers (T cells).
- To investigate the correlation of the diffuse reflectance optical spectroscopy with tumor response to PDT (**Appendix B**).

4 METHODOLOGY

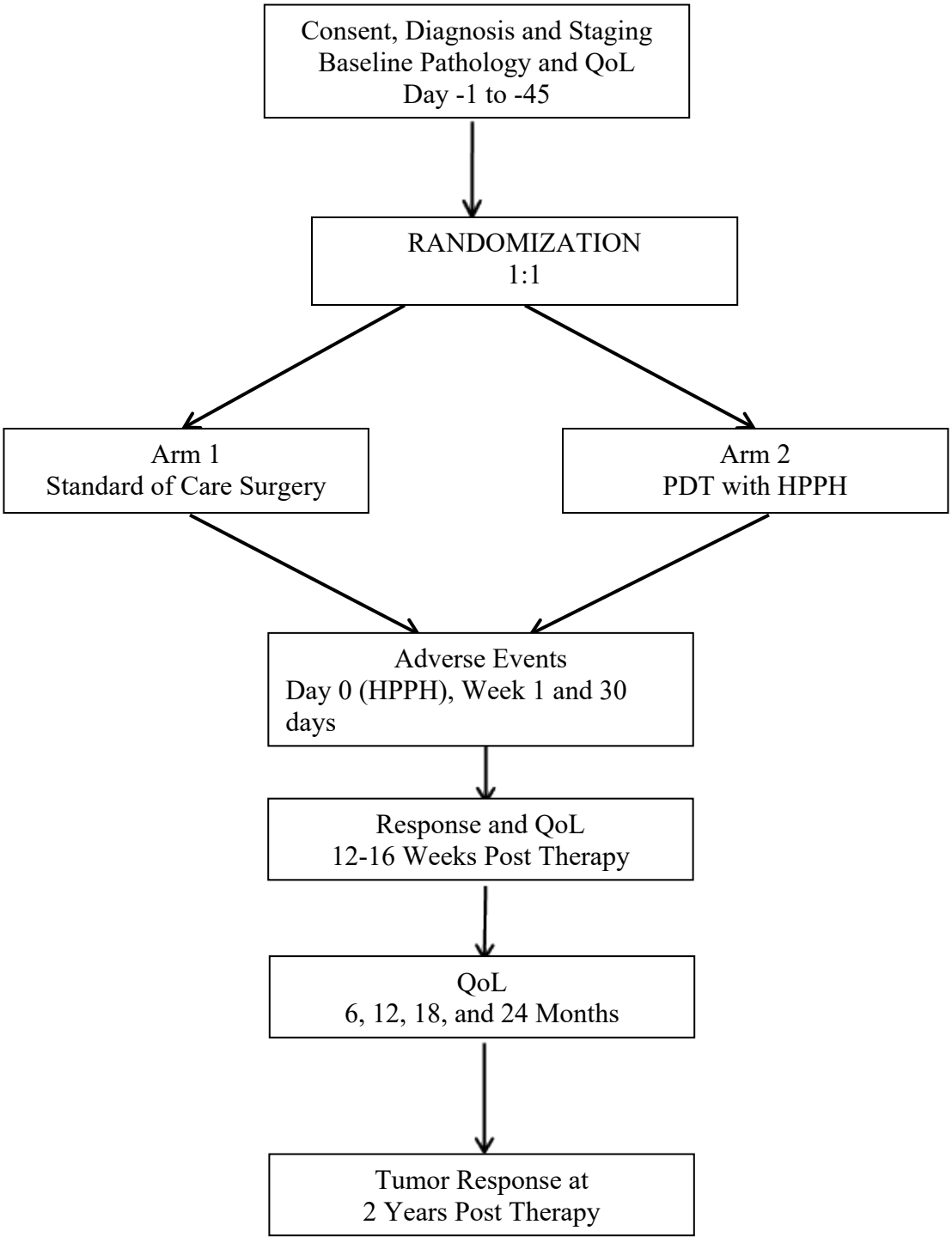
4.1 STUDY DESIGN

This is an open-label, randomized, multicenter Phase II study of HPPH-mediated PDT in participants with lesions that are diagnosed as previously untreated T1 N0 or T2 N0 SCC of the oral cavity. Participants will be randomized at a ratio of 1:1, to be treated with either surgery (57 participants) or PDT with HPPH (57 participants). The randomization will be done at RPCI by the biostatistician. The study schema is depicted in **Figure 1**.

Participants will be treated on an outpatient basis. Rarely, those undergoing HPPH with PDT may require hospitalization but this will be decided on a case by case basis. Participants undergoing surgery may be hospitalized.

4.1.1 Treatment Procedure

Figure 1. Study Schema



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For those participants randomized to HPPH with PDT, a single dose of HPPH at 4 mg/m^2 will be administered via slow intravenous (IV) infusion over 1 hour. Approximately 24 hours (± 4 hours) later, the target tumor will be illuminated with a 665 ± 3 nm laser (ML7710-665 LASER, Modulight, Inc., Tampere, Finland). A total light dose of 140 J/cm^2 at a fluence rate of 150 mW/cm^2 will be delivered with a single quartz fiber optic equipped with a micro lens (Frontal Light Distributor Model FD1, Medlight SA, Switzerland). In areas that preclude direct illumination of the lesion and margins with a microlens fiber, the light will be delivered through a cylindrical diffuser fiber with a diffuser end (Medlight SA, Switzerland) that will be inserted into a 10 mm in diameter flexible applicator (Frieburg Flap, Elekta Inc. Atlanta, GA). The Frieburg Flap is an FDA approved device designed to keep radiation source at constant distance from the treatment surface (see attached letter of approval). Multiple cylindrical fibers (in parallel) can be inserted into the flap to cover an entire tumor and margins in curved surfaces. The light through each cylindrical diffuser will be delivered at a fluence rate of 495 mW/cm (accounting for about 5% loss) to a total light dose of 462 J/cm, which is equivalent to surface illumination of 150 mW/cm^2 and 140 J/cm^2. The PDT center at RPCI will provide sections of the Frieburg Flap that will need to be sterilize prior to use, following the manufacturer instructions (see attcahed). The entire tumor and 5 mm - 10 mm margins will be illuminated. The remainder of the oral cavity will be shielded to avoid illumination of healthy tissue.

4.1.2 Post Treatment Evaluation

Participants will be scheduled to have a clinical examination at 1 week and within 4 - 6 weeks and at 12 – 16 weeks post therapy. In the event that a suspicious lesion is observed, participants will be scheduled for a biopsy at the discretion of the treating physician, at 4-6 weeks post treatment. In addition, a scheduled pathological evaluation will be conducted by taking a 3-mm punch biopsy from the treated tumor site during the clinical visit at 12-16 weeks post therapy.

Tumor response will be determined at 24 months post treatment. The treating physician will examine the clinical response and a photograph of the treatment site will be taken with paper ruler, to determine the reduction in the lesion size, according to RECIST v1.1. A biopsy may be taken, if clinically indicated. The biopsies will be processed following the standard of care pathology. A clinical pathologist will examine the processed tissue section and determine the pathological response.

Participants who have partial or no-response will be offered standard therapy, at the discretion of the treating physician.

We hypothesize that non-responders or partial responders in the PDT arm are likely to be participants whose tumor does not retain HPPH. For this subset of participants that are treated with PDT at RPCI, an additional biopsy (50 mg tissue mass) will be taken at the time of excision of the recurred tumor to evaluate cellular mechanisms that contribute to tumor retention of HPPH. The biopsy sample is immediately dropped into a sterile 15-ml screw-cap tissue culture tube containing 5 ml of serum-free RPMI medium. A set of such tubes are prepared prior to surgery and can be stored at 4°C for up to a month until use. A research nurse (or other personnel in the operating room, OR) will label the sample tube with an identifier code pertaining to the case, but without inclusion of any PHI. The tube containing the biopsy sample will be placed either into a refrigerator or bucket of ice until pick-up by a member of the investigating laboratories (Drs. Shafirstein or Baumann, as detailed below). The OR personnel will inform the research associate in the laboratories of either Dr. Shafirstein or Dr. Baumann via telephone or text message. The

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associate will pick-up the sample tube at the entrance to the OR and immediately carry it to the laboratory of Dr. Baumann, or Dr. Shafirstein.

The analysis will be performed in vitro by generating primary tumor cell culture from the biopsy material. The tumor cells will be incubated with HPPH and uptake and retention monitored over 72 hours in the live cultures by microscopic imaging. HPPH fluorescence will serve as indicator for subcellular location and concentration of HPPH.

Contact person in Dr. Baumann laboratory:
Erin Tracy
Research Associate
Department of Molecular and Cellular Biology
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, NY 14263
Tel: 716 8458175 (Office),
Cell: (716) 408-7206

Contact person in Dr. Shafirstein laboratory:
Michael Habitzruther
Research Technologist
Photodynamic Therapy Center
Department of Cell Stress Biology
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, NY 14263
Tel: 716 845 3551 (Office)
Cell: (716) 809-0365

4.2 PARTICIPANT QUALITY OF LIFE EVALUATION

Participants' QoL will be evaluated with the widely accepted University of Washington Quality of Life Questionnaire Version 4 (UW-QoLQ v4).[49,50] It has been tested in several prospective studies and found to be reproducible, reliable, and valid for head and neck cancer patients.[51] It is simple to complete, employs a simple algorithm to compute the overall score, and is easy to interpret while yielding objective results.[51] This version includes 12 individual Likert-scale items and 4 global questions. Each participant's overall score on the UW-QoLQ v4 will be calculated at baseline, at 12-16 weeks, and at 6, 12, 18, and 24 months post-PDT.

4.3 MANAGEMENT OF THE NECK AND SALVAGE SURGERY

The management of the neck will be according to standard of care, at the discretion of the treating surgeon. If the participant, based on the pathology of the neck dissection or primary oral cancer resection, has perineural invasion, extracapsular spread, or requires additional therapies including radiation or chemotherapy, they will be dropped from the study and replaced with another participant.

Participants will receive standard curative therapy 6 weeks after failing to respond to PDT with HPPH. All the participants who will have disease progression, local recurrence, or partial or no response (PR, NR) following the PDT with HPPH will be considered treatment failures. The determination will be performed during the study visits, and based on clinical exam and pathology, if clinical exam is unclear.

The surgeon will provide a surgical plan for every patient, including those randomized to PDT. If the patient requires salvage surgery post-PDT, the surgeon will compare the salvage surgery specimen diameter to the diameter of the spot size used for PDT. This data will be used to demonstrate whether PDT affects the surgical plan.

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4.4 TARGET ACCRUAL AND STUDY DURATION

A maximum of 114 participants at 3 sites, including RPCI, will be enrolled. Accrual is expected to take up to 4 years. Each participant is expected to be on the study for two years and will be followed according to NCCN guidelines.

5 PARTICIPANT SELECTION

The treating physician or his designee at each network site will determine eligibility.

5.1 INCLUSION CRITERIA

To be included in this study, participants must meet the following criteria:

1. Age ≥ 18 years of age.
2. Have an ECOG Performance Status of ≤ 2. Refer to **Appendix D**.
3. Participants with previously untreated T1/T2 N0 squamous cell carcinoma of the oral cavity with or without extension to the oropharynx.
4. Histologically confirmed squamous cell carcinoma of the target tumor(s).
5. Tumor thickness is 4 mm or less (measured clinically and/or by CT or MRI scan).
6. CT or MRI of the neck to confirm staging.
7. Tumor accessible for unrestricted illumination for photodynamic Therapy (PDT) (accessibility as determined by the physician).
8. Life expectancy of at least 12 months in the judgment of the physician.
9. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.
10. Participant or legal representative must understand the investigational nature of this study and sign an Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

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5.2 EXCLUSION CRITERIA

Participants will be excluded from this study for the following:

1. Those who have had chemotherapy or radiotherapy or targeted agents within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.
2. Those with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
3. Those with porphyria or with known hypersensitivity to porphyrins or porphyrin-like compounds.
4. WBC < 4,000.
5. Those with impaired renal and/or hepatic function (total serum bilirubin >2 mg/dL, serum creatinine > 2 mg/dL, alkaline phosphatase (hepatic) or SGOT > 3 times the upper normal limit.
6. Diagnostic biopsy reveals perineural invasion (PNI) and/or lymphovascular invasion (LVI).
7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
8. Nodal disease as detected by clinical exam or CT.
9. Pregnant or nursing females.
10. Unwilling or unable to follow protocol requirements.
11. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.
12. Received an investigational agent within 30 days prior to enrollment.
13. Trismus or compromised airway.
14. Previous treatment in the target tumor area.

5.3 INCLUSION OF WOMEN AND MINORITIES

Both men and women and members of all races and ethnic groups are eligible for this study.

For Network Sites, refer to **Appendix A** for site specific instructions.

6 INVESTIGATIONAL PRODUCTS

6.1 ACTIVE SUBSTANCE AND SOURCE

The drug (photosensitizer) to be used in this study is 2-[1-hexyloxyethyl]-2-Devinyl pyropheophorbide-a (HPPH).

The HPPH is formulated for injection as follows:

Raw Materials for HPPH Formulation

Raw Material Name	Manufacturer Name/ Part Number Supplier Name/Part Number	Quantity in 2000 gram Batch
HPPH	Syngene/S14/FP/15/00053	2.40 gm
Sterile Water for Injection, USP	VWR/B. Braun Medical/L8501-01	1862.81 gm
190 Proof Ethanol*, USP	VWR/Spectrum/ET108-1LTGL	34.36 gm
Dextrose, Anhydrous, USP multi-compendial	VWR/JT Baker/JT1920-5	98.04 gm
Sodium Carbonate, NF	VWR/Spectrum/95035-752	0.26 gm
Tween 80*, USP	VWR/JT Baker/JT4117-4	2.13 gm
Total		2000.00 gm
pH adjustment after formulation		
Phosphoric Acid, NF, FCC	VWR/JT Baker/JT0262-1	0.082 gm
Sterile Water for Injection, USP	VWR/B. Braun Medical/L8501-01	8.12 gm

*Ethanol and Tween 80 percentages are volume/volume.

The concentration of HPPH vials will be 1.13 mg/mL.

6.2 DRUG SHIPMENT

The HPPH will be provided by Photolitec (Photolitec, LLC. Buffalo, NY) and shipped frozen, on dry ice to the participating sites.

Each receiving site will document the date of receipt of the shipment. Drug shipment records will be retained by the investigational pharmacist or designee.

6.3 STORAGE, PREPARATION AND STABILITY

Stability: The current drug has been found to be stable for up to 6 months. Long-term stability studies will be ongoing during the course of this study.

Storage and Preparation: HPPH vials will be stored frozen (a standard -20 C freezer), thawed at room temperature prior to administration, dispensed by the pharmacy of participating sites and administered within 4 hours of being removed from the freezer. The final dose should be protected from light.

Documentation: A careful record of each vial dispensed (including lot number) will be maintained. This record will also include the date of drug administration and the participant ID for whom the drug was made available.

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6.4 HANDLING AND DISPOSAL

The manufacturer (Photolitic) will send the investigational drug to the RPCI research pharmacy and participating sites. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record may be reviewed by the Sponsor's staff or representative. It is the Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

Used vials (excess drug) will be destroyed according to standard practices at the site after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

Under no circumstances will the Investigator supply investigational drug to a third party or allow the investigational drug to be used in a manner other than as directed by this protocol.

6.5 THE TREATMENT LASER SYSTEM

In this study we will use a Modulight laser (ML7710-665). This is a medical laser designed for PDT. This laser system can deliver the light fluence rate (W/cm^2) and dose (J/cm^2) at the wavelength (665 ± 3 nm) required to activate the HPPH. The laser system includes a calibration port, and a SanDisk memory card for storing device history data. The PDT center at RPCI purchased this laser model for research evaluation.

The participating sites will use the same laser model and identical treatment fibers.

7 TREATMENT PLAN FOR PDT WITH HPPH:

7.1 DOSING AND ADMINISTRATION

For participants randomized to HPPH with PDT, the light and drug dose will be fixed, 150 mW/cm^2 to deliver 140 J/cm^2 of 665-nm light and 4 mg/m^2 drug, respectively. The HPPH product will be added to 100 cc intra venous (i.v.) bag of D5W and infused via i.v. pump over 1 hr.

The justifications for selecting these doses are provided in sections 1.4.1 and 1.5.1. Treatment will be administered in an outpatient basis in most cases. Reported adverse events (AEs) and potential risks are described in **Section 10.1**.

7.2 PARTICIPANT DOSE MODIFICATIONS

The drug dose and light dose will not be modified.

7.3 DURATION OF TREATMENT

Participants may remain on study in the absence of disease progression, unacceptable toxicity or withdrawal from study.

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7.4 STUDY WITHDRAWAL

Upon participant withdrawal from the study, all end of study evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF.

Reasons for study withdrawal should be classified as follows:

- Death.
- Progressive disease.
- Treatment-related toxicity.
- Toxicity unrelated to treatment.
- Investigator judgment.
- The Investigator may withdraw a participant if, in his/her judgment, it is in the participant's best interest to do so.
- Participant receives an additional adjuvant therapy.
- Noncompliance
- Participant voluntary withdrawal
- A participant may withdraw from the study at any time, for any reason. If a participant discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal.
- Participants in which the surgical pathology demonstrates perineural invasion, extracapsular spread or the participant requires additional therapy including radiation or chemotherapy.

Participants who are unavailable for follow-up evaluations should be classified as lost to follow-up for 1 of the following reasons:

- Lost to follow-up: For a participant to be considered lost to follow-up, the investigator must make two attempts to re-establish contact with the participant. The attempts to re-establish participant contact must be documented (e.g., certified letter).
- Death: Date and cause of death will be recorded for those participants who die within 30 days after last dose of study drug (telephone contact with family is acceptable).

8 STUDY PROCEDURES

Unless otherwise defined in the written protocol text, all procedures/assessments will be conducted in accordance with RPCI Clinical Research Services Standard Operating Procedures.

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8.1 PARTICIPANT RANDOMIZATION AND REGISTRATION

We will employ a web-based stratified blocked randomization scheme developed at RPCI by the biostatistician in conjunction with the GOG Foundation Statistical & Data Management Center. Participants will be randomized stratified by study site with permuted blocks of size 4 within strata and will assigned to standard of care surgery or PDT with HPPH. Study sites will need to have IRB approval entered into the system prior to accessing the randomization system. Eligibility of each participant will be established prior to randomization.

Informed consent ***MUST*** be completed prior to receiving any study related procedures.

8.2 BASELINE EVALUATIONS

The following will be performed within 1 to 45 days prior to administration of study drug or surgery:

- History, physical
- Clinical examination with photograph of lesion if possible.
- Confirm tumor staging with CT or MRI scans of the head and neck and chest.
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and height)
- Hematology [(i.e., complete blood count (CBC) with automated differential]: WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils, % lymphocyte, absolute lymphocyte, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated)
- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap)
- Biopsy (diagnosis)
- HCG urine or serum for women of childbearing potential
- Performance status (ECOG): **Appendix D**
- Evaluate lesion size
- Quality of Life Questionnaire: **Appendix H**

8.3 DAY 0 INFUSION (ARM 2 – PDT WITH HPPH)

- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight)
- Correlative studies blood samples
- HPPH infusion
- Adverse events

8.4 DAY 1 TREATMENT

- Laser PDT with HPPH (Arm 2) or Surgery (Arm 1)
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight)
- Optical spectroscopy (Arm 2)

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- Normal tissue toxicity grade (Arm 2, **Appendix F**)

8.5 ABOUT 1 WEEK POST TREATMENT

- Clinical examination with photograph of lesion if possible
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight)
- Correlative studies blood samples (for participants randomized to PDT only)
- Normal tissue toxicity grade (**Appendix F**)
- Adverse events

8.6 ABOUT 4 - 6 WEEKS POST TREATMENT

- Clinical examination with photograph of lesion if possible
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight)
- Correlative studies blood samples (for participants randomized to PDT only)
- Normal tissue toxicity grade (for participants randomized to PDT only) (**Appendix F**)
- Adverse events

8.7 ABOUT 12 - 16 WEEKS POST TREATMENT

- Clinical examination with photograph of lesion if possible
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight)
- Performance status (ECOG): **Appendix D**
- Response, clinical (for both arms)
- Response, pathological, biopsy for all participants.
- Quality of Life Questionnaire: **Appendix H**

8.8 POST-TREATMENT FOLLOW-UP EVALUATIONS

Post treatment follow-up evaluations will occur every 3 - 4 months in year 1, 3 - 6 months in year 2, per the NCCN guidelines.

- Clinical examination with photograph of lesion, if possible
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight)
- Performance status (ECOG): **Appendix D**
- Response, clinical (at each follow-up and at 2 years)
- Response, pathological, biopsy, will be performed during routine visits, only if clinically indicated
- Confirm tumor staging with CT or MRI scans of the head and neck and chest, only if clinically indicated
- Quality of Life Questionnaire at 6, 12, 18, and 24 months: **Appendix H**.

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8.9 SCHEDULE OF PROCEDURES AND OBSERVATIONS

The schedule of procedures and observations for this study is summarized in Table 2 and Table 3 below.

Table 2 Schedule of Procedures and Observations for Participants Randomized to PDT

	Baseline[1]	Day 0 Infusion	Day 1 Treatment	~1 Week Post Treatment	~4-6 Weeks Post Treatment	~12-16 Weeks Post Treatment	Follow-Up[2]
History, Physical	X						
Clinical Exam (with lesion photograph if possible)	X			X	X	X	X
Confirm tumor staging with CT or MRI scans of the head and neck and chest	X						X[10]
Vital Signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and height)[3]	X	X	X	X	X	X	X
Hematology[5]	X						
Chemistry[6]	X						
Blood Samples (if possible) for correlative studies (immune, photosensitizer & biomarker analyses [7]		X		X	X		
Biopsy (diagnosis)	X						
HCG urine or serum for women of childbearing potential	X						
HPPH Infusion		X					
Optical spectroscopy			X				
Laser			X				
Normal Tissue Toxicity Grade			X	X	X		
Performance Status/ECOG	X					X	X
Response, Clinical (Evaluate Lesion Size)	X					X	X
Response, Pathological, Biopsy						X	X[8]
Quality of Life Questions	X					X	X[9]
Adverse Events		X		X	X		

	Baseline[1]	Day 0 Infusion	Day 1 Treatment	~1 Week Post Treatment	~4-6 Weeks Post Treatment	~12-16 Weeks Post Treatment	Follow-Up[2]

1 Performed within 45 days prior to first dose of study drug.
2 These follow-up to 2 years.
3 Height collected at baseline only.
4 Blood will be collected Pre-infusion.
5 Hematology (CBC/automated differential: WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, %neutrophils, abs. neutrophils, %monocytes, abs. monocytes, %eosinophils, abs. eosinophils, %basophils, abs. basophils, %lymph T, abs. lymph T, platelet confirmation as clinically indicated, & differential confirmation as clinically indicated).
6 Chemistry (i.e., complete metabolic panel (CMP): chloride, Co2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
7 Refer to **Section 8.10**.
8 Biopsy for response will be performed during routine visits, only if clinically indicated, and at 2 years.
9 At 6, 12, 18 and 24 months.
10 CT or MRI as clinically indicated.

Table 3 Schedule of Procedures and Observations for Participants Randomized to Surgery

	Baseline[1]	Day 0	Day 1 Surgery	About 1 Week Post Surgery	About 4-6 W Post Surgery	About 12-16 W Post Surgery	Follow-Up[2]
History, Physical	X						
Clinical Exam (with photograph of lesion if possible)	X			X	X	X	X
Confirm tumor staging with CT or MRI scans of the head and neck and chest	X						X[8]
Vital Signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and height)[3]	X	X	X	X	X	X	X
Hematology[4]	X						
Chemistry[5]	X						
Biopsy (diagnosis)	X						
HCG urine or serum for women of childbearing potential	X						
Toxicity Grade				X	X		
Performance Status/ECOG	X					X	X
Response, Clinical (Evaluate Lesion Size)	X					X	X
Response, Pathological, Biopsy						X	X[6]
Quality of Life Questionnaire	X					X	X[7]
Adverse Events				X	X		

1. Performed within 12 weeks prior to surgery.
2. These follow-up visits will be according to the NCCN guidelines for T1/T2 SCC of head and neck.
3. Height collected at baseline only.
4. Hematology (CBC/automated differential: WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, %neutrophils, abs. neutrophils, %monocytes, abs. monocytes, %eosinophils, abs. eosinophils, %basophils, abs. basophils, %lymph T, abs. lymph T, platelet confirmation as clinically indicated, & differential confirmation as clinically indicated).
5. Chemistry (i.e., complete metabolic panel (CMP): chloride, Co2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
6. Biopsy for response will be performed during routine visits, only if clinically indicated, and at 2 years.
7. At 6, 12, 18 and 24 months.
8. CT or MRI as clinically indicated.

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8.10 CORRELATIVE STUDIES SAMPLE COLLECTION AND PROCESSING

8.10.1 Immune Monitoring for Isolation and Storage of Immune Cells

This assay will be performed only for participants randomized to PDT with HPPH. Whole blood samples for immune monitoring for isolation and storage of immune cells will be collected via venipuncture using (1) 10 mL green-top heparinized collection tube. If possible, sample collection will be obtained at the following time points:

- Prior to infusion of HPPH on Day 0
- About 1 week after the infusion of HPPH
- About 4 – 6 weeks after the infusion of HPPH

Whole blood samples collected at RPCI will be sent at room temperature for processing the same day of collection.

Whole blood samples collected at participating sites will be shipped at room temperature on the day of collection Monday - Thursday. Do not ship specimens on Fridays or on day before a holiday. Samples should be clearly labelled with study #, patient initials, subject ID #, date of collection, source of material, (i.e. blood, serum) and sample time point (i.e. prior to infusion of HPPH, Day 0), Each subject should have their samples entered on a Network Specimen Requistion Form (Other) provided for you along with e-mail notification to Dr. Gollnick; Sandra.Gollnick@RoswellPark.org and crsnetworkcoordinators@roswellpark.org

The samples should be sent to:

Roswell Park Cancer Institute
Attn: Flow Cytometry – I 33616
Elm & Carlton Streets
Buffalo, New York 14263
716-845 3528 (8:30 am -5 pm)
joseph.tario@Roswellpark.org and flowlab@roswellpark.org

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

8.10.2 Photosensitizer (HPPH) and Biomarker (Serum Alkaline DNase) Levels in Serum

This assay will be performed only for participants randomized to PDT with HPPH. Blood for determination of photosensitizer and biomarker levels will be collected via venipuncture using (1) 10 mL red-top collection tube. Whole blood should be allowed to clot and serum isolated via centrifugation. Caution should be used to prevent hemolysis. Sample collection will be obtained at the following time points:

- Prior to infusion of HPPH on Day 0
- About 1 week after the infusion of HPPH
- About 4 – 6 weeks after the infusion of HPPH

Whole blood samples collected at RPCI will be picked up at room temperature for processing in Dr. Bellnier's laboratory the same day of collection.

Serum will be isolated per network site's SOP specific to their centrifuge. Isolated serum samples from participating sites will be frozen at site (-80C) and stored at site until notified by Network coordinator to batch ship all three-time points for each subject. Each patient will have a Network Specimen Requisition Form (Other) filled out and included in the shipment. Ship only on Monday-Thursday. Do not ship specimens on Fridays or on day before a holiday. Samples should be clearly labelled with study #, patient initials, subject ID #, date of collection, source of material, (i.e. blood, serum) and sample time point (i.e. prior to infusion of HPPH, Day 0), with e-mail notification:

Roswell Park Cancer Institute
Department of Cells Stress Biology
Attn: Dr. David Bellnier – I 33616
Elm & Carlton Streets
Buffalo, New York 14263
716-845-7679 or 716-845-3551
David.Bellnier@RoswellPark.org and crsnetworkcoordinators@roswellpark.org

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

8.10.3 Diffuse reflectance optical spectroscopy

This assay will be performed only for participants randomized to PDT with HPPH. Non-invasive reflectance spectroscopy will be performed to assess HPPH concentration, blood volume, and blood SO2 within the lesion before and immediately after PDT. We will use the reflectance system marketed by Zenalux (Zenascope). This device has been approved by the IRB at RPCI for use in two ongoing clinical studies (I 235613 and I 239713). A short description of the system and the scientific rationale are provided in **Appendix B**.

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The measurements will be done by placing the measurement probe (5 mm in diameter) in contact with the surface of the lesion for a few seconds. The probe will deliver low-intensity white light to the lesion and detect the reflected light. A total of 3-5 measurements will be taken from the center of each lesion, before and immediately after PDT. The data set will be identified by the participant's ID and stored on a secure laptop. The end of the probe will be disinfected after use in each participant by soaking it in Cidex for 15 minutes following the procedure described in **Appendix C**.

8.11 PATHOLOGY

At each site, the tumor biopsy will be sent to a surgical pathologist and processed for routine standard of care pathological examination. When tumor-biopsy morphology precludes objective evaluation by histopathology, ancillary immunohistochemical studies may be employed to determine the presence of tumor cells, by the pathologist. (If standard H&E cannot be used to evaluate the presence of tumor cells, the pathologist will use immunohistochemistry to evaluate the biopsy).

8.12 CLINICAL

Dr. Biel, a Project Leader at the University of MN will be available for consultation throughout the study.

Ear, Nose & Throat Specialty Care of Minnesota
Dr. Merrill Biel
2211 Park Avenue South
Minneapolis, MN 55404
Tel. 612-871-2980 or Cellphone: 612-501-8535
Fax: 612-871-2012 or E-mail: bielx001@umn.edu

9 EFFICACY EVALUATIONS

9.1 OBJECTIVE TUMOR RESPONSE

Pathological tumor response will be evaluated by taking a 3-mm punch biopsy from the PDT treated or surgical area at 12-16 weeks after PDT or surgery. The participants from the PDT and surgery arms will be followed clinically up to 2 years. At the end of the follow up time, the treating physician will examine the clinical response and a photograph of the treatment site will be taken with paper ruler, to determine the reduction in the lesion size, according to RECIST v1.1. The study coordinator or nurse will take the photos. The treating physician will determine the lesion size with a caliper if photos can't be taken.

9.2 TARGET LESIONS

All identifiable lesions will be recorded with digital photography and clinical examination. The objective tumor response will be determined according to the following criteria per Recist v1.1:

- **Complete Response (CR):** Disappearance of all target lesions. Any lymph nodes must have a reduction in short axis to < 10 mm.

- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. A biopsy will be taken from the suspected lesions for histological confirmation of squamous cell carcinoma.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study, the response will be listed with stable disease. In this case, a biopsy will be taken from the suspected lesion for histological confirmation.

9.3 EVALUATION OF RESPONSE

Time point response assessments will be performed 12 - 16 weeks and 24 months after PDT. To determine time point response, refer to **Table 4** below.

Table 4 Time Point Response Criteria (+/- non-target disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

The best overall response is the best response recorded from the start of study treatment until follow-up is completed or the participant goes off study (the end of treatment taking into account any requirement for confirmation).

- **Symptomatic Deterioration:** Participants with global deterioration of health status requiring study withdrawal without objective evidence of disease progression at that time, and not related to study treatment or other medical conditions should be reported as progressive disease due to "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment due to symptomatic deterioration. Symptomatic deterioration that may lead to study withdrawal includes, but is not limited to, symptoms such as:
    - Weight loss > 10% of body weight.

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- Worsening of disease-related symptoms (e.g., worsening dyspnea, increasing pain/increasing requirement for narcotic analgesics).
- Decline in performance status of > 1 level on ECOG scale.

10 SAFETY EVALUATION

10.1 ADVERSE EVENTS

10.1.1 Definition

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite').

An AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

10.1.1.1 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

10.1.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

10.1.1.3 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

10.1.1.4 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.1.2 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 4 of the CTCAE is identified and located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology and graded according to definitions provided in the CTCAE Version 4.

The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.
- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.

- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

10.1.3 Reporting Routine Adverse Events

Table 5 Guidelines for Routine Adverse Event Reporting for Phase 2 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Routine AEs occurring between the start of intervention until 30 days after the last intervention or until the event has resolved, stabilized, death, or a new treatment is started, whichever comes first, will be reported. New information will be reported after it is received.

Photolitec, LLC. Buffalo, NY will be receiving copies of all the reports (de-identified).

10.2 SERIOUS ADVERSE EVENTS

10.2.1 Definition

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does **NOT** include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours)
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above

10.2.2 Reporting Serious Adverse Events

All new SAEs occurring from the date of the HPPH study drug infusion until 30 days after the HPPH Drug infusion, or PDT light treatment, will be reported to the IRB, in accordance to RPCI guidelines. The RPCI SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30 day follow up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAE's identified as an Unanticipated Problem by the Investigator must be reported. Please refer to **Section 10.5**for details on reporting Unanticipated Problems.

10.3 INVESTIGATOR REPORTING: NOTIFYING PHOTOLITEC LLC

The investigator at each site will notify Photolitec, LLC. Buffalo, NY on the occurrences of reportable safety issues by sending de-identified copies of the safety reports to:

Ravindra K. Pandey, PhD
Chief Scientific Officer
Photolitec, LLC
73 High Street
Room # 115
Buffalo, NY 14203
Ravindra.Pandey@RoswellPark.org
(Office Phone) 716.854.1030
(Cell phone) 716.345-9348
FAX# 716-845-8920
Secondary Photolitec Contact:
Pascal Soares, V.P Business Development
email address: Psoares@photolitec.org

10.4 FOLLOW-UP FOR SERIOUS ADVERSE EVENTS

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

10.5 UNANTICIPATED PROBLEMS

10.5.1 Definition

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:

a) The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.

b) The characteristics of the population being studied.

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed **Serious** per **Section 10.2**.

10.5.2 Reporting Unanticipated Problems

Unanticipated problem reporting will begin at the time of participant consent. The Reportable New Information (RNI) Form will be submitted to CRS Compliance Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS Compliance will submit the RNI to the IRB.

When becoming aware of new information about the Unanticipated Problem, submit this updated information to CRS Compliance with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**.

10.6 SAFETY STOPPING RULE

If 20% of patients randomized to the PDT arm fail treatment and require salvage surgery at any one institution with 50% of their accrual target, the RPCI DSMB will suspend the study for further evaluation.

10.7 FDA REPORTING

This protocol is being conducted under a RPCI IND, and RPCI will be responsible for reporting certain AEs or Unanticipated Problems to the FDA. RPCI's Compliance Office will report Network Site reports to the FDA.

The following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

Within 7 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Fatal or life-threatening.

Within 15 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Serious but not fatal or life-threatening.

Or meets **ANY** of the following criteria:

- A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).
- Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.
- Any findings from animal or in vitro testing that suggest a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.
- Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Sponsors are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

Reporting Process

The principal investigator or designee will complete and submit a FDA Form 3500A MedWatch for any event that meets the above criteria. Forms will be submitted to the CRS Compliance Office via email: CRSCompliance@RoswellPark.org.

11 DATA AND SAFETY MONITORING BOARD

The RPCI Data and Safety Monitoring Board will assess the progress of the study, the safety data, and critical efficacy endpoints. The DSMB will review the study annually and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) or termination of the study.

12 STATISTICAL METHODOLOGY

The primary objective of this study is test the non-inferiority of PDT to standard of care by comparing the rate of tumor response after PDT to those obtained after surgery, at 24 months post treatment. The secondary objectives are to compare QoL after PDT or surgery at 6, 12, 18, and 24 months post-procedure, and to assess the toxicity using the CTEP NCI Common Terminology Criteria for Adverse Events (CTCAE Version 4.0).

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12.1 JUSTIFICATION FOR THE STATISTICAL DESIGN AND THE NON-INFERIORITY MARGIN

In our previously published study we observed an 82% CR in patients with T1/T2 N0 SCC of the oral cavity treated with PDT and HPPH.[18] We also reported a similar response rate when we used HPP-PDT to treat early stage laryngeal cancer.[52] These response rates are in agreement with other studies using PDT in this indication (see **Table** 1 in section **1.3**). All patients that failed to respond were successfully salvaged by surgery. Since the local recurrence rate after initial surgery is as high as 20%,[7-9] we believe that it is reasonable to assume that 85% CR will be observed in both arms. We also wish to provide a bit of a cushion in case the surgical response rate is much higher than 85% given we are in an experimental setting.

In addition, we propose using the logic and rational the FDA guidance documents propose for traditional phase III bioequivalence trials in terms of our trial design. The FDA refers to various rules such as the 80/20 rule, 75/75 rule, where the generic drug needs to be within 20% of the brand product relative to specified pharmaceutical measures. For a phase III trial the standard 80/20 rule translates to approximately a 17 percentage point difference. The 75/75 rule yields roughly a 21 percentage point difference. Hence, in the phase II setting we believe a 20-point difference is reasonable in terms of determining whether or not a confirmatory large-scale phase III trial with a tighter equivalence window should be put forward as a next step. The information gained form this study will be used for a larger scale phase III equivalence trial in terms of planning and sample size calculations with a tighter equivalence threshold. In terms of safety, it should be noted that patients that fail PDT can be effectively salvaged with surgery, in a timely manner.

12.2 SAMPLE SIZE DETERMINATION

In the proposed randomized trial, participants will be randomized to the treatment arms using a stratified block randomization scheme, with blocking stratified by clinical site (RPCI, and two other participating sites). Participants will be included in data analyses according to their randomized treatment assignment irrespective of the treatment actually received (intent-to-treat). Exceptions would include those who withdraw their consent to use any of their data prior to receiving any study medication. Initiation of study treatment will take place as soon as possible following randomization. No method of imputation will be used for missing data. All available data from participants who fail to complete this study will be included in all safety summaries.

The safety of the interventions will be assessed through the evaluation of Grade 3 or higher toxicities deemed possibly related to treatment. Both efficacy (e.g., tumor response) and toxicity rates will be estimated using simple relative frequencies. The corresponding 95% confidence intervals for the estimated probabilities will be computed using the method proposed in Clopper and Pearson (1934).

The design for this study is based on a test for non-inferiority of PDT compared to standard of care with regards to tumor response at 24 months post-procedure. Justification for use of a non-inferiority trial is that PDT may be viewed as a potential replacement for standard of care if it is established as less toxic than the standard of care yet still providing acceptable efficacy. Let π_{SOC}

and π_{PDT} are the probabilities of tumor response in the standard of care and PDT groups, respectively. The hypotheses corresponding to the proposed non-inferiority trial are

$$H_0 : \pi_{PDT} \leq \pi_{SOC} - \Delta,$$
$$H_a : \pi_{PDT} > \pi_{SOC} - \Delta,$$

where Δ is the non-inferiority margin. Specifically, we will be using the approach of Farrington-Manning to test our hypothesis via a score based test.[53]

Under the null hypothesis ($\pi_{PDT} = \pi_{SOC} - \Delta = \pi$) is the probability of observing a particular set of results. A non-inferiority margin of 20 percentage points will be utilized and the Farrington-Manning based test will be performed in conjunction with a 0.05 nominal significance level. In the event that the non-inferiority test is statistically significant, a test for superiority will be conducted. The samples sizes of the trial are set at 57 in the standard of care and PDT groups. With the proposed sample sizes, there is approximately 80% power associated with the non-inferiority test when the true tumor response probabilities are equal to 85% in both groups. The calculation was carried forth using SAS PROC POWER.

In the analysis of QoL simple data analyses will initially take place including individual participant-level profile plots and overall mean plots used to examining the mean structure. Formal statistical examination of longitudinal patterns will be done through the use of a mixed model. Restricted maximum likelihood estimation will be utilized in the model fitting procedures as implemented by SAS PROC MIXED (version 9.3). Once the model is fit, specific linear contrasts based on the estimated model parameters will be constructed and used to test hypotheses concerning between time points and between group comparisons. We acknowledge the possibility of informative missingness, that is, the probability of a particular observation being missing may be related to the health of the participant, and therefore analyses will be interpreted with caution. All tests will be two-sided and tested at a 0.05 nominal significance level. Standard diagnostic plots will be used to assess model fit and transformations of variables may be considered in order to meet statistical assumptions.

12.3 EFFICACY ANALYSIS

Objective tumor response will be tabulated overall. All participants who will be randomized to the PDT treatment or surgery will be evaluable for response. Tumor response will be evaluated according to RECIST v1.1. The treating physician will examine the clinical response and a photograph of the treatment site/s will be taken with paper ruler, to determine the reduction in the lesion size. Tumor response will be determined according to the guidelines in sections 9.2 and 9.3.

If clinically indicated, the clinical evaluation will be confirmed with pathological examination of tissue 3-mm punch biopsy that will be taken from the treated region.

12.4 ADVERSE EVENT

The frequency of toxicities will be tabulated by grade. All participants who receive any study treatment will be considered evaluable for toxicity.

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RPCI may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

12.5 INTERIM ANALYSIS AND CRITERIA FOR EARLY TERMINATION OF THE STUDY

No interim analysis is planned for this study.

13 ETHICAL AND REGULATORY STANDARDS

13.1 ETHICAL PRINCIPLES

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

13.2 INFORMED CONSENT

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant or the participant's legally authorized representative in accordance with applicable GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

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The Investigator shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

14 STUDY RESPONSIBILITIES

14.1 DATA COLLECTION

Data entry into the database is to be completed in a timely fashion (within 30 days) after the participant's clinic visit. If an AE is considered serious it is captured on both the Adverse Event page and the Serious Adverse Event Form, which is handled in an expedited fashion).

Data management activities will be performed using EXPeRT. EXPeRT is a suite of software tools that enables the collection, cleaning and viewing of clinical trial data. CRS data management will design the study-specific database and facilitate its development by the eClinical Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database will be put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs (via EXPeRT Module). eClinical is compliant with all relevant technical aspects of relevant GCP guidelines.

- The system can generate accurate copies of stored data and audit trail information in human readable form.
- System access is limited to authorized individuals through the controlled assignment of unique ID and password combinations.
- The system is designed to periodically force users to change their passwords and verifies that user ID and password combinations remain unique.
- The system automatically generates a permanent time-stamped audit trail of all user interactions.

When data entry is complete, data management will review the data and will query any missing, incomplete, or invalid data points for resolution by the Clinical Research Coordinator and Investigator. Once all queries have been resolved, the data can be released to the statistician for analysis.

14.2 MAINTENANCE OF STUDY DOCUMENTS

Essential documents should be retained per RPCI's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with RPCI.

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15 ADMINISTRATIVE RULES

15.1 REVISIONS TO THE PROTOCOL

RPCI may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

15.2 TERMINATION OF THE STUDY

It is agreed that, for reasonable cause, either the Investigators or the Sponsor, RPCI may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, RPCI may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of patients enrolled in the study.

15.3 CONFIDENTIALITY

Any data, specimens, forms, reports, photos, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

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16 APPENDICES

Appendix A. Instructions for Network Sites

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:

Roswell Park Cancer Institute
CRS Network Office
ASB K 104
Buffalo, New York 14263

Telephone:
Monday - Friday; 8:00 AM to 4:30 PM EST
716-845-3155

After hours, weekends, and holidays request the RPCI Investigator
716-845-2300

Fax: 716-845-8743

2. INFORMED CONSENT

- Informed consent must be obtained by the site Investigator/designee from any participant, or their legally authorized representative, wishing to participate, prior to any procedures or treatment.
- An informed consent template is provided by RPCI and can be amended to reflect institutional requirements.
- All consent changes must be reviewed by RPCI Network Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that the most up to date version of the IRB approved consent is being used.
- Within 5 business days, notify the RPCI Network Office of all participant withdrawals or consent to limited study participation and appropriately document the discontinuation and the reason(s) why.

3. PARTICIPANT REGISTRATION

The participant, or their legally authorized representative, completes the **Gender, Race, and Ethnicity Form** and this is placed in the study binder.

RPCI does not grant exceptions to eligibility criteria.

Phase 2 Protocol Registration Instructions

The Screening and Enrollment Log must be faxed to the RPCI Network Office within 1 business day of the date the participant is consented. Once the Investigator has determined that eligibility has been met, complete the Subject Registration Form and fax it to the RPCI Network Monitor at 716-845-8743**.**

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Protocol Randomization Instructions

4. Patients at Roswell Park Cancer Institute will be registered directly by Roswell staff using the web-based registration system. For patients at institutions outside Roswell Park Cancer Institute, the local site staff will contact the appropriate coordinator to register the patient using the web-based registration application as developed by the GOG Foundation Statistical & Data Management Center in conjunction with the study biostatistician. Within 24 hours the Network Monitor will email the randomization arm assignment and network participant ID # back to the site PI. The site PI will send a confirmation email back to the Network Monitor verifying the randomization arm for the specified network participant. Questions regarding randomization issues can be emailed to alan.hutson@roswellpark.org or william.brady@roswellpark.org.

5. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this must be reported to the RPCI Network, site IRB and any other regulatory authority involved in the study.
- ALL study deviations will be recorded on the **Study Deviation Log**.

6. STUDY DOCUMENTATION

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The RPCI Network Monitor must be able to read what has been deleted.
  - Do **NOT** use white-out, magic marker, scratch-outs.
  - Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.
- It is the responsibility of RPCI to inform the Investigator/institution as to when these documents no longer need to be retained. If, for any reason, the Investigator desires to no longer maintain the study records, they may be transferred to another institution, another investigator, or to RPCI upon written agreement between the Investigator and RPCI.

7. DRUG ACCOUNTABILITY

Drug accountability must be strictly maintained.

- Responsibility rests solely with the Investigator but can be delegated as appropriate (e.g., to pharmacy personnel).
- A drug accountability record form (DARF) will record quantities of study drug received, dispensed to participants and wasted, lot number, date dispensed, participant ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.
- Study drug supply will only be used in accordance with the IRB approved study.

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- Drug accountability forms are protocol and agent specific, they are study source documents and will be used to verify compliance with the study.
- An inventory count must be performed with each transaction. Any discrepancies shall be documented and explained.
- Drug accountability forms must be stored with study related documents.
- Each medication provided for this study and each dosage form and strength must have its own DARF.
- Dispensing the wrong study supply is considered a **medication error**.
- **NEVER** replace investigational agents with commercial product.
- Do **NOT** "transfer", "borrow" or "replace" supplies between studies.

8. SERIOUS ADVERSE EVENT REPORTING

The site Investigator or designated research personnel will report all SAEs, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**. The site will notify the RPCI Network Monitor within 1 business day of being made aware of the SAE. A preliminary written report must follow within 1 business day of the first notification using the following forms:

- RPCI SAE Source form
- MedWatch Form FDA 3500A- This protocol is being conducted under a RPCI IND, please refer to **Section 10.7** of the protocol FDA Reporting for timelines of reporting.
- Notify Photolitec:
  Dr. Ravinda K. Pandey
  email address: Ravinda.Pandey@Roswellpark.org FAX# 716-845-8920
  Secondary Photolitec Contact:
  Pascal Soares, V.P Business Development
  email address: Psoares@photolitec.org

A complete follow-up report must be sent to the RPCI Network Monitor when new information becomes available.

9. UNANTICIPATED PROBLEM REPORTING

An unanticipated problem (UP) is any incident, experience, or outcome that meets **all** of the criteria in **Section 10.5**.1. Network sites follow the instructions below for reporting a UP to the Network monitor. RPCI compliance will report the information to the FDA.(Section 10.7)

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff from each site will notify **their local IRB in accordance with their local institutional guidelines**. The site must also notify the RPCI Network Monitor within 1 business day of being made aware of the Unanticipated Problem by completing the **RPCI Unanticipated Problem Report Form** and faxing or emailing it to the RPCI Network Monitor.

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Appendix B. Spectroscopy

In participants where the lesion location permits use of a non-invasive spectroscopy probe, quantitative diffuse reflectance spectroscopy measurements will be performed immediately prior to and immediately following PDT. The information extracted from these measurements includes hemoglobin oxygen saturation (SO_2), blood volume, and HPPH concentration.

Intriguing preliminary associations have emerged between several of these metrics and treatment response, but the small number of treatment failures precludes any firm conclusions based on our previously published Phase I results (Rigual, Shafirstein et al. Clinical Cancer Res 2013). In keeping with our central focus of establishing PDT as a mainstream option for head and neck cancer, the spectroscopy device to be deployed to sites outside of Roswell Park will be the reflectance system marketed by Zenalux Biomedical, Inc. This system is inexpensive, compact, and has been rigorously characterized by our collaborators at the University of Rochester (Drs. Foster and Baran). The Zenalux system is available widely to clinicians. It is fully capable of acquiring the reflectance data necessary to test the hypotheses that one of a combination of initial HPPH levels, blood volume, and hemoglobin oxygen saturation are useful predictors of tumor response to HPPH PDT.

Each of the above-mentioned parameters offers the potential to report something important about a tumor's amenability to PDT and/or its response to a treatment. For example, because the photochemistry of PDT relies on oxygen, one would predict that relatively high SO_2 at the time of treatment would predict for a good response. Similarly, a higher photosensitizer concentration would be an indicator that likely predicts for a favorable response. Therapy-induced reductions in tumor blood volume and the details of the time course of blood volume reduction have been useful reporters in pre-clinical models. This creates a significant clinical research opportunity to identify readily accessible, non-invasive surrogate optical reporters of treatment response, which may eventually help to identify which participants may require follow-up PDT or some other intervention following an initial treatment. Thus, there is a strong scientific rationale for the use of these forms of optical spectroscopy studies.

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Appendix C Chemical Sterilization

High Level Disinfection using Cidex, for the Frieburg Flap or reflectance spectroscopy probe that will be used in the measurements described in Section 8.10.3, will be performed with the following steps:

- Cidex must be used under a hood (ventilation hood is required): avoid inhalation.
- Wear protective gloves- do not allow to touch hands, or to splash in eyes.
- Prior to placing in the Cidex: the spectroscopy probe must be thoroughly cleaned of any debris, blood, and other bodily fluids.
- Immerse the distal end of the spectroscopy probe in Cidex solution for 15 minutes (item must be completely immersed).
- Remove from Cidex solution (wearing gloves for protection).
- Rinse the probe thoroughly with sterile water- all Cidex must be removed by rinsing.
- Pat dry with sterile towel or sterile gauze.
- Place in sterilization bag or baggie.

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Appendix D ECOG Performance Status

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

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Appendix E Toxicity Serious Adverse Event Reports

An evaluation of toxic response to HPPH administration will be performed on all participants treated under this protocol. Responses will be graded based upon the classification criteria listed in the Common Terminology Criteria for Adverse Events, Version 4.0.

The following scale will be used for systemic toxicity:

Description	Grade
Acceptable	Grade 0, Grade 1, Grade 2
Unacceptable	Grade 3 or higher

Adverse events will be graded and recorded in the electronic database. Serious Adverse Events will be reported on the SAE Reporting Form.

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Appendix F Normal Tissue Toxicity Grading

Effect	Score
No change.	0
Mild erythema and/or mild edema.	1.0
Moderate erythema and/or moderate edema (ability to eat solid foods).	1.5
Extensive erythema and/or extensive edema (requires liquid diet).	2.0
Severe edema (no alimentation possible), ulceration >>4 mm in depth (as determined by the physician).	3.0
Respiratory distress due to edema), ulceration >>4 mm in depth (as determined by the physician).	4.0

Note: In some cases the normal tissue toxicity may not be possible to judge if no normal tissue is in the light field.

Appendix G. Correlative Studies (if possible)

Examination of Induction of Anti-Tumor Immunity in Participants Treated with PDT

In order to determine whether PDT enhances anti-tumor immunity a three-pronged analysis will be performed. The effect of PDT on T cell activity will be initially be determined by examining the activation status of participant T cells before and after PDT administration. PDT induces a rapid pro-inflammatory response; such responses are associated with T cell activation and proliferation, which are frequently muted in participants with advanced cancer. T cell activation will be determined by flow cytometric analysis of peripheral blood T cells. Using T cell subtype and activation specific profiles, this analysis will allow us to determine whether administration of PDT alters both the activation status and ratio of T Cell subtypes present before and after therapy.

The phenotypic characterization described above will determine whether PDT affects T cell activation and subtype ratio but will not discern whether the effects are tumor specific. Most tumors over-express p53 and many head and neck tumors overexpress HPV 16. Examination of changes in the immune response to p53 and/or hpv 16 can reveal changes in tumor specific immune responses. To examine whether PDT enhances the immune response to p53 or HPV 16, peripheral blood T cells will be isolated and exposed to p53 and HPV 16 ex vivo. The ability of each participant's T cells to respond will be measured over time and compared against pre-treatment results and to their ability to respond to antigens they have previously been exposed to, i.e., cytomegalovirus, Epstein-Barr virus and influenza virus (the so-called memory mix).

The second method for examining tumor specific T cells following PDT involves adding an additional marker to the flow panels described above. There is a well-defined p53 immune epitope that binds to the human major histocompatibility complex molecule HLAA2. Greater than 40% of the patients at RPCI express HLA-A2. HLA-A2 expression status of the trial participants will be determined. T cells isolated from HLA-A2+ participants will be tested for p53 reactivity using a flow cytometry reagent known as a tetramer that allows identification of p53 specific T cells.

The methods described above will determine whether PDT enhances T cell responses. To determine whether there is an increase in humoral (B cell) responses to tumors following administration of PDT changes in the levels of circulating antibodies against p53 and HPV 16 will be measured. (Network sites to inform Dr. Sandra Gollnick and crsnetworkcoordinators@roswellpark.org and ship to Flow Cytometry - see shipping instructions in section 8.10.1). Do not ship specimens on Fridays or on a day before a holiday.

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Appendix H Appendix H. **University of Washington Quality of Life Questionnaire version 4 (UW-QoLQ v4)**

Date: ___/___/____ Subject ID#_____

This questionnaire asks about your health and quality of life over the past seven days. Please answer all of the questions by checking one box for each question.

1. Pain (Check one box:)

I have no pain.

There is mild pain not needing medication.

I have moderate pain - requires regular medication (codeine or nonnarcotic).

I have severe pain controlled only by narcotics.

I have severe pain, not controlled by medication.

2. Appearance (Check one box:)

There is no change in my appearance.

The change in my appearance is minor.

My appearance bothers me but I remain active.

I feel significantly disfigured and limit my activities due to my appearance.

I cannot be with people due to my appearance.

3. Activity (Check one box:)

I am as active as I have ever been.

There are times when I can't keep up my old pace, but not often.

I am often tired and have slowed down my activities although I still get out.

I don't go out because I don't have the strength.

I am usually in bed or chair and don't leave home.

4. Recreation (Check one box:)

There are no limitations to recreation at home or away from home.

There are a few things I can't do but I still get out and enjoy life.

There are many times when I wish I could get out more, but I'm not up to it.

There are severe limitations to what I can do, mostly I stay at home & watch TV.

I can't do anything enjoyable.

5. Swallowing (Check one box:)

I can swallow as well as ever.

I cannot swallow certain solid foods.

I can only swallow liquid food.

I cannot swallow because it "goes down the wrong way" and chokes me.

6. Chewing (Check one box:)

I can chew as well as ever.

I can eat soft solids but cannot chew some foods.

I cannot even chew soft solids.

7. Speech (Check one box:)

My speech is the same as always.

I have difficulty saying some words but I can be understood over the phone.

Only my family and friends can understand me.

I cannot be understood.

8. Shoulder (Check one box:)

I have no problem with my shoulder.

My shoulder is stiff but it has not affected my activity or strength.

Pain or weakness in my shoulder has caused me to change my work.

I cannot work due to problems with my shoulder.

9. Taste (Check one box:)

I can taste food normally.

I can taste most foods normally.

I can taste some foods.

I cannot taste any foods.

10. Saliva (Check one box:)

My saliva is of normal consistency.

I have less saliva than normal, but it is enough.

I have too little saliva.

I have no saliva.

11. Mood (Check one box:)

My mood is excellent and unaffected by my cancer.

My mood is generally good and only occasionally affected by my cancer.

I am neither in a good mood nor depressed about my cancer.

I am somewhat depressed about my cancer.

I am extremely depressed about my cancer.

12. Anxiety (Check one box:)

I am not anxious about my cancer.

I am a little anxious about my cancer.

I am anxious about my cancer.

I am very anxious about my cancer.

Which issues have been the most important to you during the past 7 days?

Check up to 3 boxes.

Pain	Swallowing	Taste	
Appearance	Chewing		Saliva
Activity	Speech	Mood	
Recreation	Shoulder		Anxiety

GENERAL QUESTIONS

Compared to the month before you developed cancer, how would you rate your health-related quality of life? (check one box:)

Much better

Somewhat better

About the same

Somewhat worse

Much worse

In general, would you say your health-related quality of life during the past 7 days has been: (check one box:)

Outstanding

Very good

Good

Fair

Poor

Very poor

Overall quality of life includes not only physical and mental health, but also many other factors, such as family, friends, spirituality, or personal leisure activities that are important to your enjoyment of life. Considering everything in your life that contributes to your personal well-being, rate your overall quality of life during the past 7 days. (Check one box:)

Outstanding

Very good

Good

Fair

Poor

Very poor

Please describe any other issues (medical or nonmedical) that are important to your quality of life and have not been adequately addressed by our questions (you may attach additional sheets if needed).

Signature_____

Printed name_____

Date_____

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